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Isoxsuprine infusion in the rat: Alterations in maternal, fetal and neonatal glucose homeostasis*

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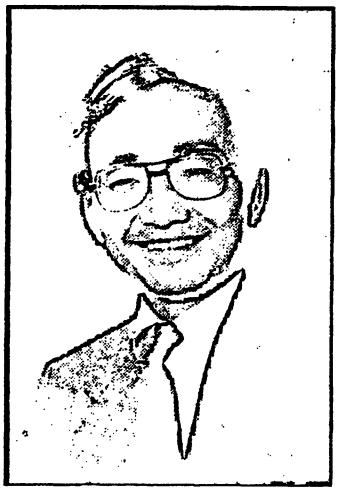
1 Introduction

Isoxsuprine and other sympathomimetic drugs are now frequently used to inhibit premature labor [4, 9, 15, 16, 17]. The tocolytic properties of these agents are attributed to their B_2 stimulatory effect which reduces the strength and frequency of contraction of uterine muscle. While much of the cardiovascular effects of these agents upon the mother and fetus has been identified [3, 5, 6, 21], less is known about their effect upon glucose metabolism. **Neonates delivered of women who received B sympathomimetic drugs are at increased risk of developing hypoglycemia** [2, 7]. Several alterations in fetal and maternal glucose homeostasis may be related to this development. Maternal and fetal hyperglycemia has been reported to develop with the administration of B sympathomimetics to women [18, 26]. The increase in fetal glucose may be a direct drug effect upon the fetus as suggested by the observation that fetal hyperglycemia develops during infusion of fenoterol directly to the sheep fetus [6]. EPSTEIN et al. found elevated insulin concentrations in the cord plasma of infants whose mothers had received B-sympathomimetic agents and suggested that **fetal hyperglycemia resulting in excessive insulin production might be responsible for neonatal hypoglycemia** [7]. Because of the morbidity which results from hypoglycemia, further elucidation of the means by which B sympathomimetic tocolytic agents alter glucose metabolism seemed warranted. For this reason, this study has employed the unrestrained, awake rat model to determine the effects of isoxsuprine infusion upon the glucose and insulin production of the mother, fetus and neonate.

Curriculum vitae



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2 Materials and methods

2.1 Animals

Primiparous pregnant and age-matched virgin females were obtained from Charles River Laboratories, Wilmington, Massachusetts. The pregnant

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rats had been mated at 47 days of age and this was designated as day 0 of gestation (Gestational period = 21½ days). On day 15 of gestation, rats were anesthetized with an intraperitoneal injection of chloral hydrate (30 mg/100 g body weight) and a pre-formed silastic catheter was implanted in the jugular vein. The catheter was placed subcutaneously with the distal end sutured to the dorsum of the rat's neck. The catheter was filled with 0.1 ml of polyvinylpyrolidone containing heparin (.65 mg polyvinylpyrolidone was mixed with 1 ml of 0.9% saline and 25 units heparin) [22]. This polymer maintains catheter patency for a week or more and is aspirated from the catheter at time of infusion. Only rats who consistently grained weight following catheterization (pregnants, 10 g/day; virgins, 3–5 g/day) were studied. In addition, for maternal and neonatal studies, only rats which had 8 to 12 pups in a litter were used. All rats had ad libitum access to food (Purina Rat Chow). Pregnant rats weighed 301 ± 20 and virgin rats 268 ± 18 grams at time of infusion.

2.2 Infusion and newborn care

Rats were infused at 0900 of day 21 of gestation. Pregnant and age-matched virgin received either isoxsuprine (Vasodilan, MEAD JOHNSON, Evansville, Indiana) or 0.04 M saline. Isoxsuprine was administered as a bolus (0.11 mg/100 gram body weight) followed by a continuous infusion (0.11 mg/100 gram body weight/hour) for 3 hours to pregnant and virgin rats. Control pregnant and virgin rats received 0.04 M saline in volumes equivalent to the isoxsuprine solutions. Isoxsuprine concentration was .33 mg/ml in 0.04 M saline. Thus, depending upon body weight, pregnant rats received from 0.9 to 1.1 ml fluid as a bolus and from 2 to 3.4 ml during the 3 hour infusion. Virgin rats received from 0.7 to 1.0 ml fluid as a bolus and 2 to 3 ml during infusion. Experiments were performed with individual pumps for each rat. All infusions were conducted at room temperature (22–24 ° C).

Doses for isoxsuprine administration in humans vary from 3–6 mg for loading and 6–18 mg/hr for maintenance. Drug therapy must be individualized because of cardiovascular effects. To determine doses for the rats in this experiment, the effect of isoxsuprine upon blood pressure was established in preliminary experiments. The systolic blood pressure of restrained, pregnant and virgin rats ranged from 50–70 torr as measured with a Rodent Programmed Electro Sphygomanometer (PE-300, NARCO BIOSYSTEMS Inc., Houston, Texas) calibrated to 100 torr. Pregnant and virgin rats who received maintenance doses of 0.16 mg/100 g/hour or greater became pale and inactive and had systolic blood pressures of 30–40 torr. Rats receiving the 0.11 mg/100 g/hr maintenance dose consistently maintained blood pressures of 50–60 torr. For this reason, the latter dose, which is 10 times greater than the dose recommended for humans, was used for the entire experiment.

Rats were attached to pump tubing by means of a swivel and harness so that they were allowed unrestrained activity. Prior to and at intervals during the infusion, blood samples were obtained from the cut tail tip. The tip of the tail was gently rewarmed at each sampling to establish free blood flow. Rats were decapitated at the end of the infusion, and fetuses and placentas removed from the uterus. The umbilical cords were immediately cut, the pups dried and placed in an incubator set at 36 °C and 50% humidity. All rat pups weighed between 5.2–5.8 grams and placentas 0.6–.07 grams. To insure uniformity of measurements, only pups from litters with 8 to 12 pups were used. The weight and the appearance of the pups suggested that they were at term gestation.

Blood was collected from newborn rat pups by cutting the axillary vessels and collecting free flowing blood in heparinized tubes. One or two pups from each litter were killed at each point so that serial measurements of offspring from one mother could be made during the neonatal period.

Maternal and newborn liver samples were immediately frozen in liquid nitrogen.

2.3 Analysis

Plasma glucose concentrations were determined with a BECKMAN II Glucose Analyzer and insulin concentrations by a modification of the technique of SOELDNER and SLONE [25]. Hepatic glycogen

concentrations were determined by the method of VAN HANDEL [27].

Plasma isoxsuprine concentrations were determined by NUCLEAR MEDICAL SYSTEMS, Inc., Newport Beach, California with a double antibody radioimmunoassay technique. Plasma was initially treated with diethyl ether to extract protein since isoxsuprine is predominantly protein bound.

Eight virgin and sixteen pregnant rats were included in each of the saline and isoxsuprine infused groups. More pregnant rats were required because serial measurements of glucose and insulin were made from litter mates of isoxsuprine or saline infused mothers and limited amounts of blood could be obtained from each rat pup. Values for metabolic variables in newborn rats represent serial measurements from pups of individual litters. Eight litters are represented in the serial measurement of each variable.

Plasma samples from an additional 4 maternal rats and their offspring were analyzed for plasma isoxsuprine determination.

The "Student's" unpaired T test was used to compare differences between groups and the paired T test for differences within groups. Data are presented as the mean ± SEM [23].

3 Results

Isoxsuprine infusion did not result in any deaths, and all rats displayed apparently normal activity during infusion. None of the pregnant rats delivered during infusion of either isoxsuprine or 0.04 M saline.

Fig. 1 indicates changes in plasma glucose concentrations in pregnant and virgin rats. Before infusion, pregnant rats had a mean plasma glucose of 99 ± 7 mg/dl. This was significantly less than values for virgin rats (120 ± 8 mg/dl, $p < 0.01$). **Isoxsuprine infusion increased plasma glucose concentrations in both pregnant and virgin rats, and virgin rats receiving isoxsuprine demonstrated greater increases above preinfusion values than pregnant rats.** In both pregnant and virgin rats receiving isoxsuprine, plasma glucose concentrations tended to decrease during the 3 hour infusion however, the values at 180 minutes were not significantly less than the 30 minute values.

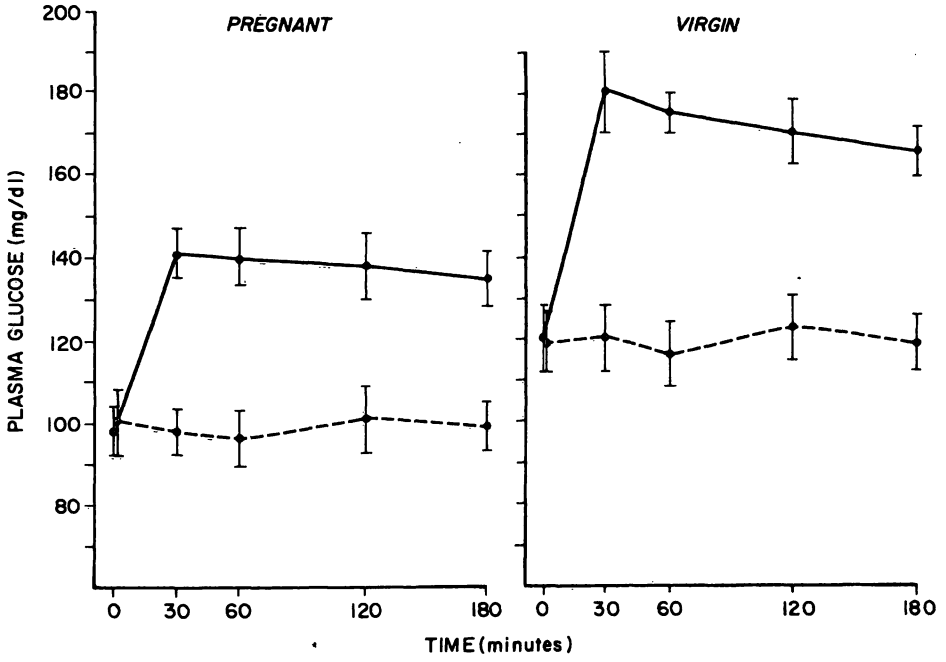

Fig. 1. Plasma glucose concentrations in pregnant and virgin rats infused with isoxsuprine (solid line) or 0.04 M saline (dotted line). Before infusion, pregnant rats had significantly lower plasma glucose concentrations than virgin rats ($p < 0.01$). Isoxsuprine infusion resulted in significant increases in plasma glucose ($p < 0.001$) above saline infusion values in both pregnant and virgin rats. Values for virgin rats during isoxsuprine infusion were significantly greater than for pregnant rats ($p < 0.001$). Values for saline infused virgins remained significantly greater than for saline infused pregnant rats ($p < 0.05$). Eight rats were included in each of the virgin groups and 16 rats in each of the pregnant groups.

Pregnant rats had significantly greater plasma insulin concentrations before infusion than virgin rats (Fig. 2). **Isoxsuprine infusion was associated with a significant increase in plasma insulin in both pregnant and virgin rats.** Thirty minutes following initiation of isoxsuprine infusion, pregnant rats demonstrated a 35% increase and virgin rats a 60% increase in insulin concentrations. Values in isoxsuprine infused rats remained elevated throughout the infusion.

At the end of the infusion, liver glycogen concentrations in rats who received saline were equivalent (pregnant 36 ± 4 mg/g wet liver and virgin 40 ± 6 mg/g wet liver). **Rats who received isoxsuprine had significantly less hepatic glycogen** and values were equivalent in pregnant and virgin rats (18 ± 8 mg/g wet liver and 16 ± 8 mg/g wet liver respectively.

Tab. I presents measurements from newborn rat pups of maternal rats who were infused with either isoxsuprine or saline. **Pups of isoxsuprine infused mothers had significantly greater plasma glucose concentrations at birth and at 1 and 4 hours of age** compared to pups of saline infused mothers. By 7 and 11 hours, glucose concentrations were significantly less in the pups of isoxsuprine infused mothers. By 16 hours of age, both groups had very low glucose concentrations which did not differ.

Hepatic glycogen concentrations were significantly less in pups of isoxsuprine infused mothers than of saline infused mothers at birth and a 1 and 4 hours of age. Values for both groups decreased significantly from preceding values at 7 hours and there were no differences in the very low values at 11 and 16 hours.

Plasma insulin concentrations were elevated in pups of isoxsuprine infused mothers at birth and at 1 hour of age. No difference in insulin concentrations occurred after this point.

Isoxsuprine concentration was determined in serial plasma samples from 4 pregnant rats and their offspring. Thirty minutes after administration of the leading dose and following initiation of the infusion, plasma isoxsuprine concentrations were 33,893 ± 4301 pcg/ml (range 25,500–39,725 pcg/ml). By 60 minutes, values were somewhat less (28,589 ± 2810 pcg/ml, range 25,660–34,208 pcg/ml). Values at 180 minutes were similar (29,808 ± 2033 pcg/ml, range 24,560–35,400 pcg/ml).

Plasma concentrations in newborn rat pups at delivery were 25,762 ± 4370 pcg/ml (range 19,330 –30,303 pcg/ml). These values were 80 to 86% of the maternal values at time of delivery. At 4 hours concentrations had decreased to 19,934 ± 5910 pcg/ml (range 16,543–23,400 pcg/ml). By

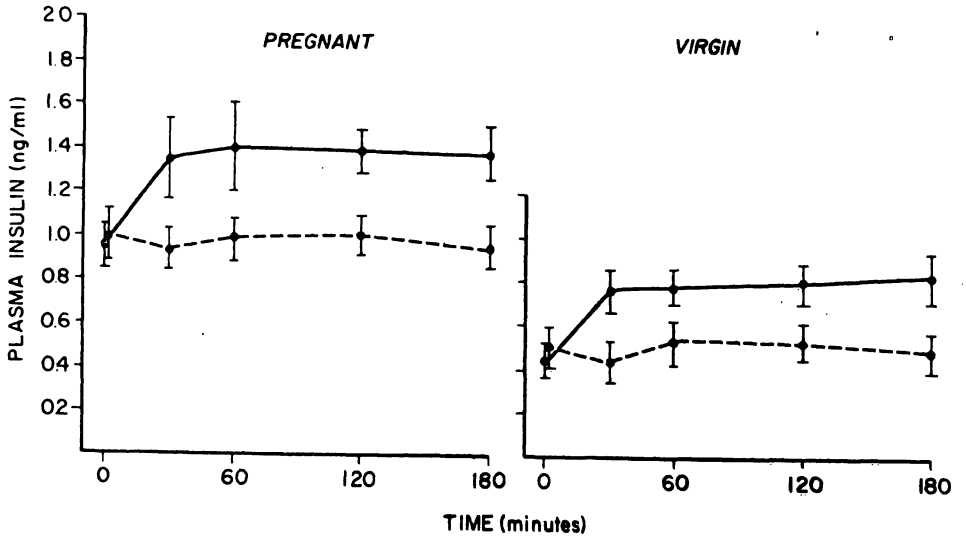

Fig. 2. Plasma insulin concentrations in pregnant and virgin rats infused with isoxsuprine (solid line) or 0.04 M saline (dotted line). Before infusion, pregnant rats had significantly greater plasma insulin concentrations than virgin rats ($p < 0.01$). Isoxsuprine infusion resulted in a significant and sustained increase of plasma insulin above saline infusion values in both pregnant and virgin rats ($p < 0.01$). Eight rats were included in each of the virgin groups and 16 rats in each of the pregnant groups.

Tab. I. Metabolic variables in rat pups of isoxsuprine and saline infused mothers

	Age (Hours)					
	0	1	4	7	11	16
Glucose (mg/dl)						
Isoxsuprine	90 ± 5 ***	80 ± 8 ***	53 ± 7 **	30 ± 7 **	20 ± 6 *	20 ± 8
Saline	54 ± 5	30 ± 8	34 ± 8	60 ± 8	40 ± 5	18 ± 7
Hepatic glycogen (mg/g wet liver)						
Isoxsuprine	40 ± 9 ***	35 ± 8 ***	28 ± 6 **	18 ± 5	6 ± 1	6 ± 1
Saline	80 ± 12	64 ± 3	58 ± 6	18 ± 6	6 ± 1	4 ± 1
Insulin (ng/ml)						
Isoxsuprine	8.4 ± .2 ***	8.0 ± .5 **	2.0 ± .3	1.0 ± .3	1.1 ± .3	.7 ± .2
Saline	6.2 ± .3	1.7 ± .3	1.3 ± .4	1.2 ± .4	1.3 ± .4	.6 ± .1

* The asterisks denote degrees of difference between isoxsuprine and saline infused pups (*** - $p < 0.001$; ** - $p < 0.01$; * - $p < .05$)
Serial measurements in litter mates from 8 maternal rats are included in each group.

16 hours, values were 14,350 ± 2000 pcg/ml (range 11,303–16,101 pcg/ml).

4 Discussion

The intent of this study was to measure the short term effects of isoxsuprine administration upon maternal and neonatal glucose metabolism. **This study in some ways mimics the clinical situation in which tocolytic therapy is administered to the woman in premature labor but fails to prevent delivery.** We used the laboratory rat because in some aspects of metabolic development, the rat pup at term is similar to the premature human neonate. With respect to glucose metabolism, both have poorly developed hepatic and renal enzyme systems for glucose production and both have limited ability to mobilize insulin [11, 13, 14, 24]. We should also point out that the isoxsuprine dose used in this study far exceeded the recommendations for tocolytic therapy in humans; however, our experimental animals did not develop hypotension.

Isoxsuprine infusion to the maternal and nongravid rats almost immediately increased plasma glucose concentrations. The associated decrease in hepatic glycogen indicates that enhanced glycogenolysis is at least partly responsible for this glycemic response. While the exact mechanism by which isoxsuprine stimulates glucose production is unknown, the results of a study by ESTEBAN-ALTIRRIBA et al. [8] suggest that the glycemic effect represents a direct beta stimulation of glucose production by isoxsuprine. They found that the glucose mobilizing effects of ritrodrine, a beta sympathomimetic drug similar to isoxsuprine, can be blocked by the administration of practolol, a beta agonist. The present study suggests that isoxsuprine did not stimulate glucose production by inhibiting pancreatic insulin production since maternal insulin concentrations actually increased with infusion. **The increase in insulin thus represents a response to glucose production and may also represent a direct stimulation of the pancreatic insulin production of isoxsuprine** [10].

Isoxsuprine administration reduced hepatic glycogen concentrations to equivalent degrees in both

pregnant and nongravid rats. These values were extremely low and indicate that **3 hours of isoxsuprine infusion almost completely depleted hepatic glycogen in both pregnant and nongravid rats.** Pregnant rats, however, did not increase plasma glucose concentrations as much as nongravid rats. This suggests that the pregnant rat had greater demands upon its glucose reserve than the nongravid and most likely represents the continous drain of glucose by conceptus. The lower glucose and higher insulin concentrations in the fed pregnant rat compared to the virgin rat agree with earlier reports [19]. This observation is also consistent with the concept that the state of pregnancy results in a drain of maternal glucose to the conceptus and that "extra" maternal insulin is necessary to preserve maternal glucose stores [20].

The documentation of substantial concentrations of isoxsuprine in fetal plasma at delivery indicates that maternal administration can result in isoxsuprine delivery to the fetus. Rat pups delivered of isoxsuprine infused mothers had significantly greater glucose concentrations and lower hepatic glycogen concentrations for the first 4 hours of life than pups of saline infused mothers. Since isoxsuprine was present in neonatal plasma, these observations suggest that **isoxsuprine might have directly stimulated glycogenolysis in the rat fetus. This in utero depletion of glycogen would then be responsible for the significant decrease in neonatal plasma glucose which occurred at 7 hours of age.**

Another potential mechanism for the development of the decrease in newborn plasma glucose concentrations was the isoxsuprine stimulation of maternal glucose production which resulted in increased availability of maternal glucose to the fetus and stimulation of fetal insulin production. This possibility would agree with the findings of EPSTEIN et al. [7] who reported that infants of women who received B sympathomimetic therapy had elevated insulin concentrations in cord blood. It is unclear however whether hyperinsulinism contributes to the development of hypoglycemia in the neonate since in this study, hyperinsulinism did not continue beyond 4 hours of life. Likewise, insulin measurements at the actual time of isoxsuprine-associated hypoglycemia have not been reported in human neonates.

Newborn rat pups of isoxsuprine infused mothers had a significant decrease in plasma glucose concentration at 7 hours of age and had significantly less hepatic glycogen stores at birth compared to rats of saline infused mothers. This suggests that **in utero depletion of hepatic glycogen stores was responsible for the development of relative hypoglycemia at 7 and 11 hours of life in the offspring of isoxsuprine treated rats.** By 11 hours of age, rat pups of saline-infused mothers had also depleted their hepatic glycogen stores and by 16 hours of life, demonstrated a profound increase in plasma glucose. These changes are similar to observations by GIRARD et al. [12] who also demonstrated that during fasting in the neonatal period, rats mobilize glycogen to maintain glucose homeostasis but are unable to perform gluconeogenesis despite having an adequate quantity of gluconeogenic enzymes. Since premature human infants also are limited in their ability to perform gluconeogenesis, it is possible that human neonates of isoxsuprine treated mothers become hypoglycemic because of in utero glycogen depletion.

The limited preliminary values showing that rat pups at birth had plasma isoxsuprine concentrations approximately 80 to 86% of maternal concentrations shows that much placental transfer of this substance occurred during 3 hours of infusion. The lower concentrations at 16 hours of age suggest that the newborn rat pups can clear isoxsuprine from the intravascular space. The mechanism of this process is unknown.

It has been suggested that if B sympathomimetic therapy stimulates fetal hyperglycemia and hyperinsulinism, prolonged therapy might result in fetal macrosomia. BLOUN et al. [1] tested this hypothesis by administering ritrodrine orally to women with normal carbohydrate metabolism from the 25th week of gestation until delivery. None of the offspring of these women demonstrated increased birth weight. This study did not address this particular question since isoxsuprine was administered acutely to maternal rats at term. Under this situation, the offspring of isoxsuprine and saline infused rats did not differ in weight.

A variety of cardiovascular effects of maternal B sympathomimetic administration have been described [3, 5, 6, 21]. Uterine blood flow usually increases and systemic blood pressure may be unaffected or decrease. By adjusting isoxsuprine doses, this study attempted to avoid this latter complication. The role of these cardiovascular alterations in affecting glucose delivery to the fetus and altering fetal glucose homeostasis remains unknown.

These findings suggest **that maternal isoxsuprine infusion depletes maternal and fetal hepatic glycogen stores and that the resultant hyperglycemia stimulates maternal and fetal insulin production. The in utero depletion of hepatic glycogen stores initially causes hyperglycemia and places the newborn rat pup at risk of later developing hypoglycemia.** A similar sequence of events might be responsible for the development of hypoglycemia in the human offspring of isoxsuprine-infused mothers. Clinical studies including frequent measurement of plasma glucose and insulin concentrations and assessment of glucose turnover would be necessary to answer this question.

Summary

To determine the mechanism of alteration in glucose homeostasis associated with maternal isoxsuprine administration, isoxsuprine or 0.04 M saline was administered intravenously for 3 hours to term pregnant and age-matched virgin rats. **Isoxsuprine infusion significantly increased plasma glucose and insulin concentrations and decreased hepatic glycogen stores in both.** Compared to rat pups of saline infused mothers, pups of isoxsuprine infused mothers had significantly elevated plasma glucose concentrations for the first 4 hours of life and plasma insulin concentrations for the first two. Plasma glucose concentrations for the offspring of isoxsuprine treated mothers then decreased significantly and remained so until 16 hours of age. Hepatic glycogen concentrations were significantly less in rat pups of isoxsuprine treated mothers at birth and for the first 4 hours of life. In a limited number of studies, isoxsuprine was present at birth in substantial quantities (80–85% of maternal levels) in the plasma of rat pups of isoxsuprine infused mothers. **These data suggest that maternal isoxsuprine therapy mobilizes hepatic glycogen and results in maternal hyperglycemia. Maternal isoxsuprine infusion may directly deplete fetal hepatic glycogen and result in transient fetal and neonatal hyperglycemia.** The in utero depletion of glycogen and possibly, the early stimulation of insulin production may be responsible for the later significant decreases in plasma glucose in the offspring of isoxsuprine treated mothers.

Keywords: Glucose, hepatic glycogen, insulin, Isoxsuprine, maternal and neonatal rat.

Zusammenfassung

Isoxsuprine Infusion in Ratten. Einfluß auf das mütterliche, fetale und neonatale Glukose-Gleichgewicht

Um die Einwirkung der mütterlichen Isoxsuprin-Infusion auf das Glukose-Gleichgewicht zu untersuchen, wurde Isoxsuprin oder eine 0,04 M Kochsalzlösung über 3 Stunden intravenös an trächtige und gleichaltrige jungfräuliche Ratten verabreicht.

In beiden Gruppen wurde durch die Isoxsuprininfusion die Blutzucker- und Insulinkonzentration signifikant erhöht und die Leberglykogenmenge erniedrigt. Im Vergleich mit den neugeborenen Ratten der mit Kochsalz behandelten Gruppe, hatten die neugeborenen Ratten der mit Isoxsuprin behandelten Gruppe einen signifikant höheren Blutzuckerwert während der ersten 4 Lebensstunden und eine erhöhte Insulinkonzentration während der ersten 2 Lebensstunden. Der Blutzuckerwert der neugeborenen Ratten der Isoxsuprin-behandelten Gruppe fiel dann rasch ab und blieb so in den ersten 16 Lebensstunden. Die Glykogenkonzentration in der Leber war signifikant niedriger bei der Geburt und in den ersten 4 Lebensstunden in neugeborenen Ratten der Isoxsuprin-Gruppe. In einer kleinen Anzahl von Studien konnte Isoxsuprin bei der Geburt im Serum von neugeborenen Ratten, deren Mütter Isoxsuprin bekommen hatten, nachgewiesen werden (80–85% der mütterlichen Konzentration).

Diese Ergebnisse lassen vermuten, daß eine mütterliche Isoxsuprin-Therapie Glykogen aus der Leber freisetzt, gefolgt von einer mütterlichen Hyperglykämie. Eine Isoxsuprin-Infusion der Mutter kann den Glykogengehalt der fetalen Leber verringern, gefolgt von einer fetalen und neonatalen Hyperglykämie.

Die Senkung des Glykogengehaltes in utero und möglicherweise die frühe Anregung der Insulinproduktion könnte für den späteren Abfall des Blutzuckerwertes in den Nachkömmlingen der Isoxsuprin-behandelten Mütter verantwortlich sein.

Schlüsselwörter: Glukose, Insulin, Isoxsuprine, Leberglykogen, mütterliche und neugeborene Ratten.

Résumé

Infusion d'isoxsuprine chez le rat: Altérations de l'homeostase glucosique maternelle, foetale et neonatale

Pour déterminer le mécanisme de l'altération de l'homeostase glucosique due à l'administration d'isoxsuprine chez la mère, on administre par voie i.v. pendant 3 heures de l'isoxsuprine où 0,04 M de serum physiologique à des rats vièrges et enceintes du même âge. **Dans les deux groupes l.isoxsuprine a fait augmenter de façon significative la concentration de glucose et d'insuline** dans le plasma et fait diminuer le glycogène hépatique. En comparant les jeunes rats nés de mères perfusées au serum physiologique avec les jeunes rats nés de mères perfusées à l'isoxsuprine ces-derniers avaient une glycémie élevée pendant les 4 premières heures de leur vie et une concentration d'insuline élevée dans le plasma durant les 2 premières heures.

La glycémie des jeunes rats nés de mères traitées à l'isoxsuprine a diminué de façon significative et s'est maintenue jusqu'à leur 16 heures de vie.

La concentration de glycogène était nettement plus basse chez les jeunes rats nés de mères traitées à l'isoxsuprine à la naissance et durant les 4 premières heures de vie. Dans un nombre limité d'études, l'isoxsuprine était présent à la naissance dans le serum des jeunes rats (68–85% de la concentration maternelle) dont les mères avaient été perfusées à l'isoxsuprine. **Ce résultat laisse pensé qu'une therapie à l'isoxsuprine chez la mère mobilise le glycogène hépatique et provoque une hyperglycémie chez cette dernière. L'infusion d'isoxsuprine chez la mère peut directement diminuer le glycogène hépatique foetale avec comme résultat une hyperglycémie foetale et neonatale transitoire.** Il est possible que la diminution du glycogène au niveau uterin et la stimulation préalable de la production d'insuline soient responsable de la diminution consécutive du glucose plasmatique chez les jeunes rats nés des mères traitées à l'isoxsuprine.

Mots-clés: Glucose, glycogène, hépatique, insuline, isoxsuprine, jeunes rats, rats mères.

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